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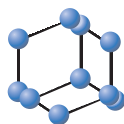
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A Historical Review of Persian Medicine Studies into Saliva Manifestations for Potential Applications for Diagnosis and Management of Metabolic Syndrome



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Abstract: Background and Objectives: Regarding the development of diagnostic tests based on saliva and the prevalence of metabolic syndrome (MetS), the aim of this study is to review Persian Medicine manuscripts in the field of saliva manifestations, its relation to metabolic syndrome, and treatment recommendations.

Methods: This study is a mini-review. We investigated the canon of medicine and some important Persian medical or pharmaceutical manuscripts from the 9th to the 19th centuries. PubMed and Google Scholar databases were explored for finding relevant information about the relationship between saliva and metabolic syndrome and its treatment.

Results: Studies have suggested that maldigestion is one of the important causes of MetS. Sialorrhea may be an early symptom of maldigestion. Attention to sialorrhea and its treatment may be useful in the prevention and treatment of metabolic syndrome based on PM sources. In PM, sialorrhea is treated with 3 major approaches: lifestyle modification along with simple or compound medicines.

Conclusion: Saliva manifestations could be considered as early symptoms of metabolic syndrome. As mentioned in WHO strategies, traditional medicine can be used along with modern medicine due to its effectiveness in the management of various ailments.

Keywords: Salivomics, xerostomia, sialorrhea, iranian traditional medicine, mizaj, temperament, avicenna, metabolic map.

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1. INTRODUCTION

Oral fluid is usually referred to as the whole saliva which contains secretions from salivary glands, upper gastrointestinal, respiratory tracts, and crevicular fluid [1]. The total volume of saliva secreted amounts to 1-2 Lit per 24 h [2]. The salivary flow rate and protein concentration show circadian variations [2]. The flow of saliva is higher in response to parasympathetic stimulation, while alpha-adrenergic stimulation and beta-adrenergic stimulation lead to the secretion of a fluid with high protein and mucin content, high viscosity, and foamy appearance [2]. Although the glandular activities are principally regulated by nerves, recent findings consider the influence of gastro-intestinal hormones, age, gender, temperature, and many drugs on salivary flow rate, composition, and metabolism. It is addressed with a focus on

xerostomia and sialorrhea [3]. Many local or systemic conditions such as menopause, obesity, and aging are represented by changes in saliva flow or composition, so, these changes are useful as risk indicators and for monitoring the overall health [1, 4-6].

Multiple functions of saliva are essential for proper protection and functioning of the body as a whole and for the general health [7]. A large number of diseases and medications can affect salivary secretion through different mechanisms leading to salivary gland dysfunction including xerostomia or sialorrhea [7]. The interaction between saliva manifestations and systemic diseases, especially in association with metabolic syndrome has been previously established [8-10]. Regarding the development of diagnostic tests based on saliva and salivomics translation of personalized medicine from concept to clinical application, it is necessary for clinicians to have a good knowledge of the clinical manifestations of saliva in clinics [11].

Considering the increasing prevalence of metabolic syndrome as well as its difficult diagnosis and treatment in the

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early stages, awareness of health care professionals about the systemic complications which may change saliva condition, can lead to a proper intervention before any invasive or stressful treatment. It will improve preventive strategies without increasing healthcare costs [12].

Persian Medicine (PM) is considered as a holistic personalized medicine aiming at preventing and diagnosing the diseases at early stages. In PM, saliva is an important diagnostic key which can give important information about healthy and diseased state [13-16]. Temperament or *Mizaj* is a fundamental concept in the school of PM. Each person has a unique characteristic called *Mizaj* which is recognized and classified according to morphological, physiological, and psychological features [17, 18]. PM considers four humors in the body while every humor has a specific temperament. Normally, there are four humors in the human body: phlegm or *Balgham*, blood or *Dam*, yellow bile or *Safra*, and black bile or *Sauda*. Each one comprises a pair of qualities as follows: cold and wet, hot and wet, hot and dry, and cold and dry, respectively [18, 19]. Every humor is a substance made from digestion and transformation of foodstuff in the gastrointestinal system [3]. Any qualitative and/or quantitative imbalance in the body temperament and humors could result in different kinds of diseases [20].

The aim of this study is to review some important PM texts especially the canon of medicine by Avicenna in order to find relevant information about saliva manifestations, discuss its relationship with metabolic syndrome, and put forward treatment recommendations.

2. METHODS

In this literature research, we investigated some of the important Persian medical and pharmaceutical manuscripts from the 9th to the 19th century CE. They included the Canon of medicine (Avicenna, 980-1037 AD), Al Havi (Rhazes, 864-930 AD), Al-Tasrif (Al-Zahrawi, 936-1013 AD), Zakhireye Kharazmshahi (Jorjani, 1042-1137 AD), Al-Mujaz fi al-Ttibb (Ibn AL-Nafiss, 1210-1288 AD), Sharh Al-asbab va Alamat (samarghandi, 1301-1500 CE), Kholasatol Hekmah (Aqili, 1701-1800 CE), Tebbe Akbari (Arzani, 1701-1800 CE), and Exir-e-Azam (Azam Khan, 1801-1900 CE). The identification of medicinal herbs has been discussed in Makhzan-ol-advieh (Storehouse of Medicaments, written by Aghili Khorasani in the 18th century CE). These books are identified as PM references in medicine and pharmacy and currently, are used as reference books in the Persian medicine and pharmacy PhD curriculum in Iran. A search was done with the terms saliva, dryness of the mouth and tongue (jefaf-e-lesan), sialorrhea, hypersalivation or ptyalism and drooling (ehragh-e-righ). Electronic databases including PubMed, Scopus, and Google Scholar were explored to find out any relationship between saliva and metabolic syndrome as well as its treatment.

3. RESULT

PM practitioners believe that maldigestion will ultimately cause the production of abnormal humor which affects the organ's function [18]. The effects of abnormal humors appear in all body fluids and waste materials including saliva,

blood, urine, and feces. They argue that any change in the quantity (as in xerostomia or hyper salivation) or quality (such as increasing or decreasing concentration) of saliva may be associated with the production of abnormal humors which is considered an important diagnostic clue [13, 14]. In PM texts, xerostomia has been defined as a subjective feeling of dry mouth; wetness of the mouth as hypersalivation or subjective feeling of excessive saliva; and ehragh-e-righ as sialorrhea or saliva drooling from the mouth during sleep or wakefulness or while speaking [21]. They believed that xerostomia and sialorrhea are associated with certain abnormalities in the mouth and salivary glands, or in other organs, such as the brain, stomach, and liver. Accordingly, its treatment depends on treating the disease of the related organ [15].

In PM, dry mouth is divided into two types: real and non-real or false xerostomia. In real xerostomia, the body's fluid is low; consequently, the salivary flow is also be very low. This type is due to the hotness and dryness of temperament. On the other hand, in non-real types, salivary flow is not low; instead, it is thick (which might be associated with a change in the composition of saliva) and this is the reason for dry mouth feeling in this type of xerostomia [13, 22]. The signs and symptoms of each type are mentioned in Table 1. There are also two types of hyper-salivation or sialorrhea: diurnal and nocturnal type. Diurnal type itself is categorized into three subtypes based on deterioration in hunger state or after the meal. The etiology, as well as signs and symptoms of each type are mentioned in Table 2.

Sialorrhea can occur in relation to various neurologic disorders and infections as well as a relatively unknown condition called idiopathic paroxysmal sialorrhea [23, 24]. Some studies have reported that sialorrhea, which is an important symptom in many inflammatory diseases, may be an early symptom of Sjögren's syndrome, too [24].

In some investigations, the relationship between metabolic syndrome and dystemperament has been reported [25]. In PM, sialorrhea is one of the most important symptoms of excess moisture in cold and/or wet dystemperaments [13-15]. The recommended traditional medicine may be useful in sialorrhea treatment, especially in idiopathic cases.

According to PM texts, causes of increased moisture in the body which can create cold and wet temperament include: those kinds of food and spices which possess cold and wet qualities increasing coldness and wetness in the body, overeating and maldigestion (which can cause accumulation of undigested materials as waste products and fat in vessels or around the tissues), and tasks which can increase wetness of the body such as excessive resting or inactivity, etc. Each one of the abovementioned causes can lead to wet dystemperament of the body and consequently, hypersalivation or sialorrhea can occur.

Moreover, in some studies, a relationship has been reported between fatty liver and cold or wet dystemperaments [26, 27] which may result in constipation [28]. Regarding the prevalence of fatty liver as a priority in healthcare systems and its role in metabolic syndrome, attention to sialorrhea and its treatment should be considered in future studies.

Table 1. Type, etiology, and clinical manifestations of xerostomia based on PM.

Type	Etiology of Xerostomia	Sign and Symptoms	References
Real dry mouth	Hot or dry dystemperament	Villi bumps over tongue, Lack of saliva, Yellowish tongue/ Intense thirst/ Yellow urine/ Strong pulse	[13, 14, 29]
	Hot Dystemperament of kidney	Polydipsia/ Polyurea/ Discolored urine	[30]
	Dehydration	-	[30]
Unreal Drymouth	1-Catarrh 2-Viscose or tick humor	Viscose and thick humidity on tongue surface or mouth, Intensifying of dry mouth with cold-tempered materials such as cold water	[13, 14, 29]

Table 2. Type, etiology, and clinical manifestations of sialorrhea based on PM.

Type	Etiology of Sialorrhea	Sign and Symptoms	References
Head and neck	Catarrh	Rhinorrhea and salivation with other catarrh sign and symptoms	[13, 31]
	Wet or cold dystemperament	Rhinorrhea and salivation with catarrh sign and symptoms, head heaviness, sharp senses	[13]
	Oral rash	-	[30]
Stomach	Hot and wet dystemperament	Aggravation of hunger, reduced satiety, salivation in sleep and on awakening, intolerance of foods and drug with hot temperament, loss of appetite	[13-16, 29]
	Cold and wet dystemperament	Maldigestion, thick and viscose saliva, sour taste in the mouth, aggravation of satiety, thirst reduction with hot temperament foods, intolerance to foods and drugs with cold temperament, improvement after vomiting	[13-16, 29, 30, 32]
	Gastric maldigestion	Flatulence, unpleasant taste in the mouth	[13]
Liver	Liver maldigestion	Flaccidity, eye inflation, poor complexion blood dilution, discolored urine, bloody shaped stool	[14]
Intestine	Intestinal worms	Salivation in sleep but dry mouth on awakesness	[13, 29]
Other	Heat dominance	Craving for sour things Or fasting	[13, 15, 16]

3.1. Treatment Approaches

The management of sialorrhea covers 3 main approaches [15]:

1. Lifestyle modification.
2. Administration of simple herbal medicines and other natural remedies.
3. Pharmaceutical formulations of two or more bioactive substances.

3.1.1. Lifestyle Modification

Lifestyle in PM refers to the six essential factors as preventive health measures for maintaining the health. The aim of lifestyle modification in sialorrhea is to reduce excess moisture in the body. For achieving this aim, following recommendations should be observed:

3.1.1.1. Air: Living in Areas with Less Humidity.

3.1.1.2. Food and Drink

- A. Eating habits modification:
- Perfect chewing

- Avoiding overeating, prolonged starvation, intense mental and physical activity after the meal, eating yogurt or drinking water along with food especially chilled water, having tea or fruit immediately after a meal.

B. Food Recommendations:

- Digestive foods, such as flesh of small birds like partridge and quail, grilled chicken and barbecue
- Quince or ginger jam
- Fruits and vegetables such as currant, celery and carrot

C. Abstinenes or regimens:

- Foods with delayed digestion like beef, matzo, kachi (containing flour, sugar and oil), cookie, fatty frozen fries, and date

3.1.1.3. Sleep and Awakeness

Sleep reduction, especially sleeping during the day or between the dawn of the fajr and sunrise, and sleeping after the meal.

3.1.1.4. Retention and Disposal of Waste or Essential Products

Avoiding excessive sexual intercourse and constipation.

3.1.1.5. Activity and Relaxation

More exercise.

3.1.1.6. Mental Status

Doing exciting activities, reduction of stressors [15].

3.1.2. Simple Medicines

Simple medicines are single minerals, botanicals, or animal ingredients which are prescribed after life style modifications [33]. In PM manuscripts, many plants are recommended in various forms of medication for treating sialorrhea. Some of these simple medicines, known as digestive agents with dry temperament, are more important with common use (Table 3). It should be kept in mind that according to the recent studies in traditional medicine, maldigestion is one of the most important reasons for MetS [18, 19, 25, 27, 34].

3.1.3. Compound Medicines

The third line of treatment in PM is the administration of compound medicines consisting of two or more ingredients

in various pharmaceutical dosage forms. Each component of these formulations possesses either synergistic effects or reducing the side effects of the others [33]. In case of resistance of sialorrhea to simple medicines, compound medications are used as the next line of management, such as the following:

- ❖ Oral administrations of Celery (*Apium graveolence*) with Ajwain (*Trachyspermum ammi*) [63]
- ❖ Combination powder of the above formula with Anis (*Pimpinella anisum*), cumin (*Cuminum cyminum*) and fennel (*Foeniculum vulgare*)
- ❖ A type of oxymel containing quince juice, ginger and honey
- ❖ Confection of *Etrifel Saghir* (the combination of honey and *Terminalia chebula Retz*, *Terminalia bellerica Roxb* and *Phyllanthus emblica L*) [64]
- ❖ Compound honey syrup (the combination of honey and the extract of the following medicinal plants: mastic, ginger, cinnamon, saffron, cardamom, and galangal Gargling [65]
- ❖ *Jullab* syrup, consisting of several ingredients (almost all recipes include saffron, rose water, white rock candy, and water) [66]

Table 3. Herbal medicines used in the management of sialorrhea and metabolic syndrome.

Plant Part	Qualities in PM	Some Pharmacological Activities	Common Name	Scientific Name	Traditional Name
Resin	Hot/dry	Anti-tumor, activity [35] Antibacterial [35, 36] Anti-inflammatory [35, 36]	Mastic	<i>Pistacia Lentiscus</i>	Mastaki
Resin	Hot/dry	Antibacterial [37], Antineoplastic [38] Antithrombotic [39]	Frankincense	<i>Boswellia Serrata</i>	Kondor
Flower Buds	Hot/dry	Antioxidant [40], Antineoplastic [41] Anti-inflammatory [42], Antifungal [43]	Clove	<i>Syzygium Aromaticum</i>	Qaranful Or Mikhak
Fruit	Hot/dry	Antioxidant [44], Antimicrobial [45] Anti-inflammatory [46]	Ajwain	<i>Trachyspermum ammi</i>	Zenian
Fruit	Cold/dry	Antioxidant and anti-ulcerative [47]	Quince	<i>Cydonia oblonga</i>	Safarjal
Seed	Hot/dry	Antioxidant [48], Anti-diabetic [49] Anti-inflammatory [50]	Cumin	<i>Cuminum Cuminum</i>	Carvey
Fruit	Hot/dry	Antithrombotic [39], Anti-inflammatory [51], Antioxidant [52, 53] Neuroprotective [52, 53]	Celery	<i>Apium Graveolens</i>	Karafs
Fruit	Hot/dry	Antioxidant [54], Anti-inflammatory [55] Hepatoprotective [56], Neuroprotective [57]	Anise	<i>Pimpinella Anisum</i>	Anisum
Leaves	Hot/dry	Antimicrobial [58] Antispasmodic [58] Anti-inflammatory [59] Antioxidant [60]	Peppermint	<i>Mentha Piperita</i>	Nana
Leaves	Hot/dry	Antioxidant [61], Antimicrobial and Anti-inflammatory [62]	Thyme	<i>Thymus Vulgaris</i>	Za'atar

- ❖ Syrup of squill oxymel: formulation of squill (*Drimia Maritima Stearn*) in the oxymel [67]

4. DISCUSSION

Based on the PM theories, any disturbance in humor production processes will be represented in saliva manifestations due to the systemic effect of humors. This is in accordance with the metabolic map of body in saliva.

Anything including any person has a unique temperament [15, 21]. Some factors such as season, geographic location, age, and gender have certain temperaments. Indeed, temperament is the final average quality (with two aspects of hotness/coldness and wetness/dryness) as the consequence of different factors.

Regarding salivation, daily circadian low flow occurs during the early morning, while it peaks during the late evening. Yearly circadian low flow occurs during the summer, while the maximum flow is observed during the winter. In PM, winter and cold weather deteriorate cold temperament and salivation [13, 14]

The secretion of saliva is controlled by a salivary center composed of nuclei in the medulla however, there are specific triggers for this process include mechanical (the act of chewing), gustatory, and olfactory stimuli. Other factors affecting secretion include psychological factors, certain types of medication, and various local or systemic diseases affecting the glands.

According to PM, some factors, such as temperament of food, odor, drug, humor, dystemperament of gastrointestinal system especially stomach, psychological factors, and physical activity also affect the secretion of saliva [16, 21].

In conventional studies, hypersalivation has two types:

- ❖ **Physiological:** Other effects of circadian rhythm, thermal stimuli, such as ice-cold drinks induce the secretion of a greater volume of saliva in comparison to hot drinks [68]. Other examples include: salivatory reflex in response to a meal (mechanoreceptors, gustatory receptors, olfactory receptors and nociceptors), citric acid, due to nausea or swallowing of very irritating food.
- ❖ **Pathological** i.e. cerebral palsy, or other severe neurological disorders [69].

From the perspective of PM, all of the abovementioned causes have the potential to cause cold and/or wet dystemperament in the body and consequently, induce sialorrhea. Worthy of note is that the main cause of paralysis in PM is thick humors or waste materials, such as phlegm in nerve root or intracellular space [13, 22].

CONCLUSION

This study provides a historical perspective of Persian medicine regarding salivary production and metabolic syndrome and put forward some information about potential applications of saliva for diagnosis and management of the metabolic syndrome. Chronic diseases like metabolic syndrome have a high burden [70]. According to WHO's strategy, traditional medicines should be conjugated to conven-

tional medicine until 2023 as integrative medicine in clinical research in order to find more efficient and safer treatments [71]. Considering the fact that metabolic syndrome is a disease related to lifestyle [72], attention to primary sign or symptoms such as sialorrhea, life style modification, and use of simple or compound formulations could be useful in the management metabolic syndrome.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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